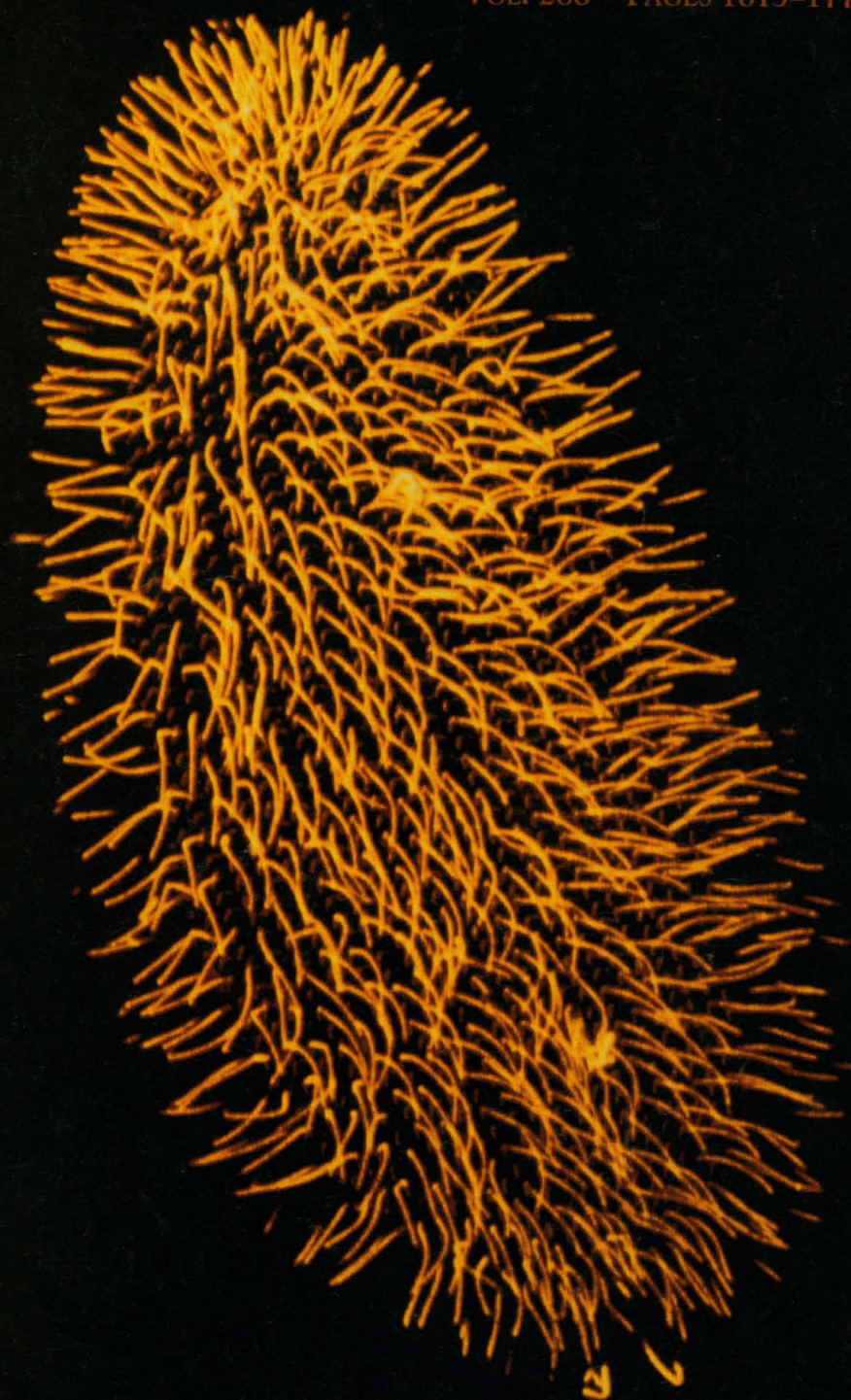


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1. Lundberg, K.S., et al. (1991) Gene 108: 1-6

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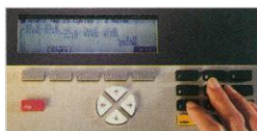
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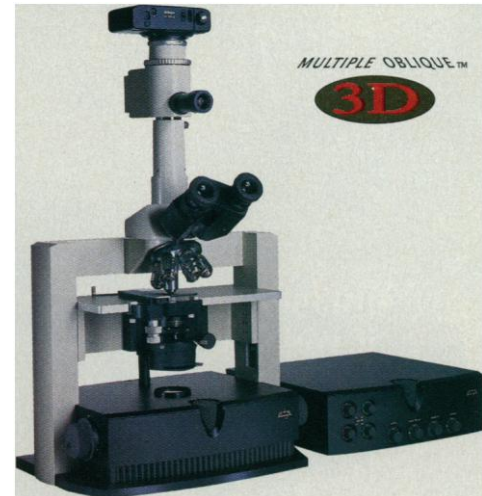
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NEUROBIOLOGY

Specimen: Thick section of cerebellum showing purkinje cells.

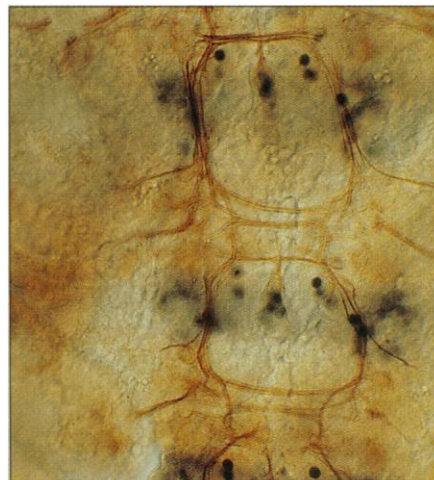
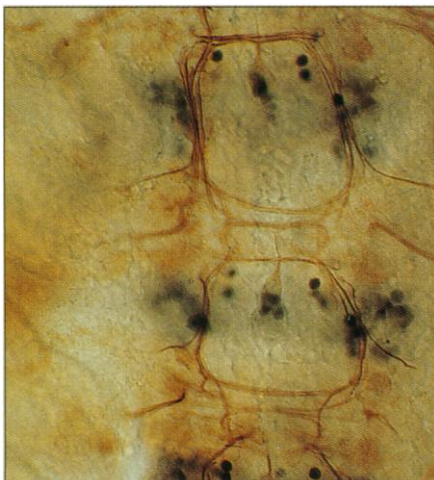
Approx. 50 –75 μm thick.

Objective: Plan Apochromat 40x dry

Qualities: Extraordinary depth of field with large stereo parallax allows tracing path of dendritic spines. High contrast without loss of resolution brings out fine details in spines.

Gary Greenberg, Ph.D.,

Edge Scientific Instrument Corp.



DEVELOPMENT

Specimen: Grasshopper embryonic ventral nerve cord, stained for axons (brown) and transcription factor engrailed (black).

Approx. 80 μm thick.

Objective: Plan Apochromat 20x

Qualities: 3D perspective distinctly separates out the various dorsal and ventral aspects of the nervous system in the developing grasshopper.

Dr. Barry Condrón, Cal Tech

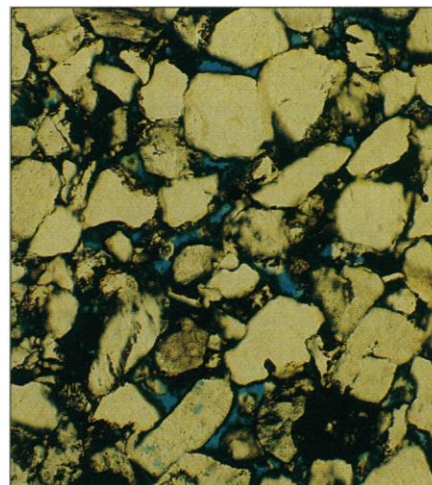
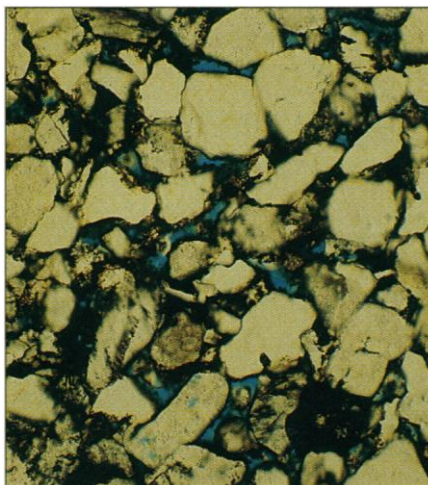
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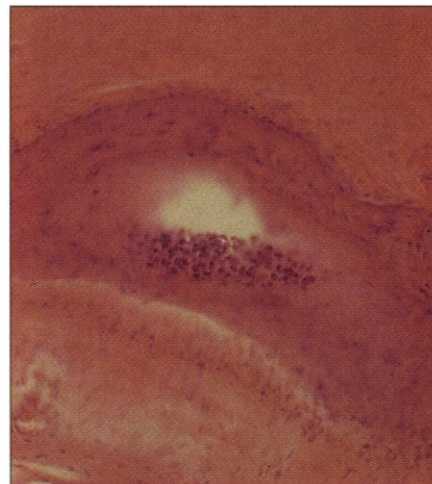
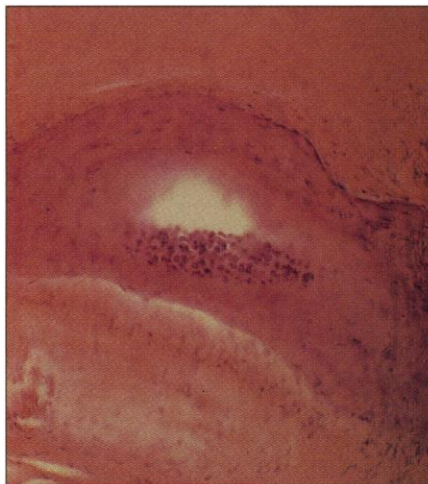
Specimen: Thin section of Jurassic Norphlet Sandstone, offshore Gulf of Mexico, showing quartz grains coated with black pyrobitumens.
Objective: Plan Apochromat 20x
Qualities: 3D perspective permits volume evaluation of infiltrated epoxy (blue).



PATHOLOGY

Specimen: Bone from rat recipient of limb transplant, undergoing lethal graft-versus-host disease. Approx. 40 µm thick.
Objective: Plan Apochromat 20x
Qualities: 3D perspective reveals fibrous matrix bone spicule and bone canal with infiltrating mononuclear cells.

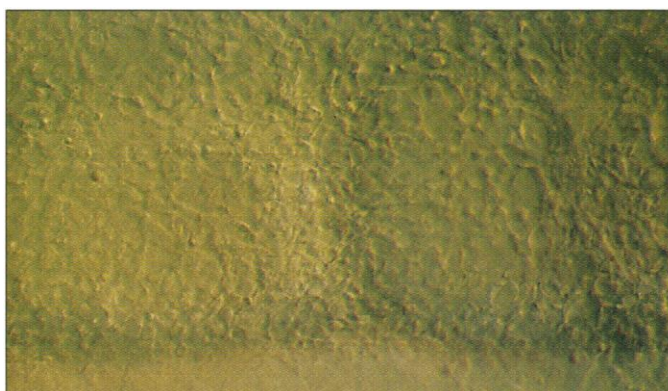
Charles W. Hewitt, Ph.D., UMDNJ –
Robert Wood Johnson Medical School



WHOLE MOUNTS

Specimen: Close up of two somites of living, unstained chick embryo (HH stage 11).
Objective: LWD 40x dry
Qualities: Even with such a thick sample, superb sharpness and high contrast of individual cells is evident.

Gary Greenberg, Ph.D.,
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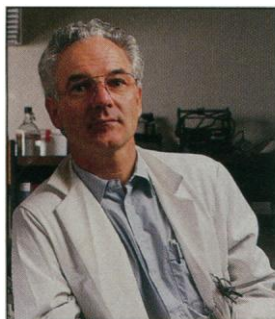
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Duesberg and AIDS

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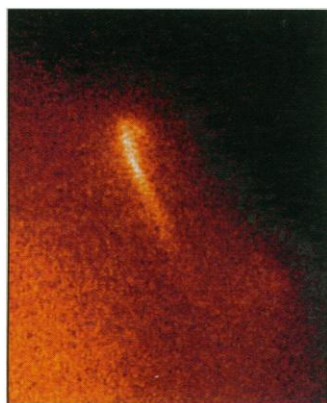
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Bright lights, big planet

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COVER

Paramecium cilia stained with an antibody that recognizes tubulin posttranslationally modified by the addition of multiple glycine units. Tubulin is the most abundant component of microtubules, which participate in many processes including cell division and cell motility.

The polyglycine modification was found on flagellar and ciliary forms of tubulin. (*Paramecium* is ~100 micrometers long.) See page 1688. [Photo: A. Fleury, Laboratoire de Biologie Cellulaire, and M. Laurent, Service d'Imagerie Cellulaire, Orsay, France]



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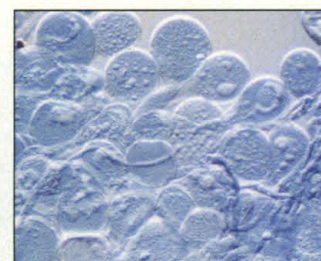
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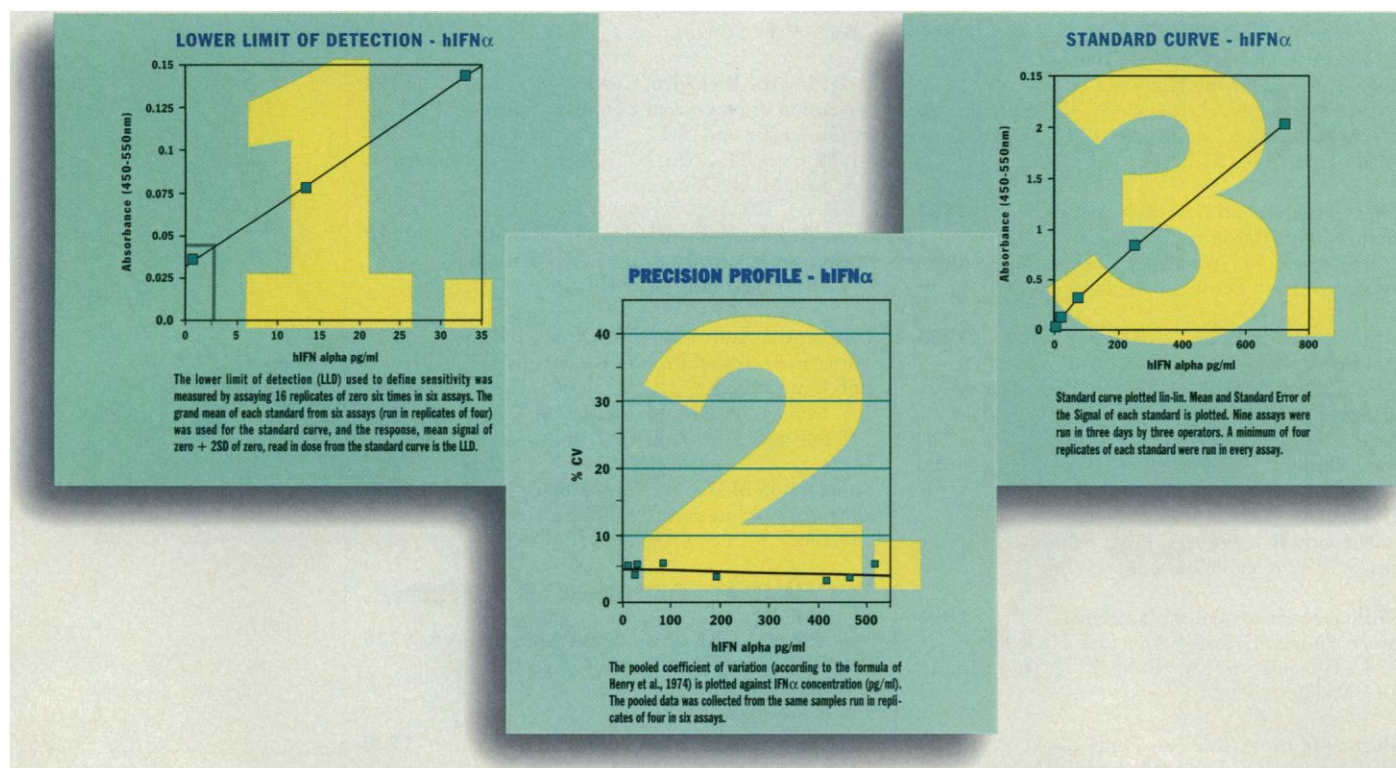
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Noblesse oblige

A good deal of recent attention has attached to a few dramatic cases of unethical scientific behavior and indeed outright fraud, but in their Policy Forum (p. 1660), Alberts and Shine focus on subtler but perhaps more widespread erosions of scientific integrity. They emphasize that scientists themselves have the primary responsibility to promote, foster, and particularly teach ethical behavior.

The O in core

The Earth's core is mainly iron, but the inferred core density seems to require the presence of a lighter element, such as oxygen. Understanding the core requires knowledge of crystal structures and properties of iron compounds at high pressures. Fei and Mao (p. 1678; see Perspective by Bassett, p. 1662) used a diamond cell apparatus and synchrotron x-ray diffraction measurements to investigate the structure of FeO under core conditions. FeO transforms to the NiAs structure at high pressures, and thus behaves more like a metal. This transition would increase the solubility of oxygen in iron, permitting a less dense core.

Going into graphite

The electronic properties of a solid can be modified by doping it with different elements. In graphite, carbon can be replaced by hexagonal boron nitride, which has a similar structure but a much larger band gap. Stephan *et al.* (p. 1683) produced graphite and carbon nanotubes doped with boron and nitrogen, using a modified electric-arc nanotube synthesis. The rapid synthesis of this

The northern lights of Jupiter

Both Jupiter and Earth exhibit aurorae in their upper atmospheres, but because the magnetospheric dynamics of the two planets are different, it has been questionable whether their aurorae share related mechanisms. Solar wind effects on the Earth's magnetosphere make terrestrial aurorae exclusively nighttime phenomena, but on Jupiter the solar influence is much less, and aurorae occur equally at day or night. Using the Hubble Space Telescope, Gérard *et al.* (p. 1675) made ultraviolet observations of an unusually bright Jovian aurora, tracking it for more than 20 hours. Their results suggest that the aurora was due to electron precipitation along magnetic field lines, as on Earth.

material in the plasma discharge may kinetically stabilize its formation, as carbon-boron-nitrogen phases are normally unstable when heated slowly to high temperatures.

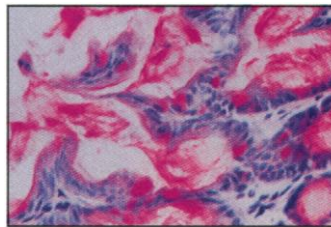
Living together

Attine (leaf cutting) ants live symbiotically with certain fungi: The fungi are essential to the ants' diet, and the ants provide the fungi with a substrate on which to grow. Hinkle *et al.* (p. 1695) and Chapela *et al.* (p. 1691) have examined the evolutionary relationship between ants and fungi by analyzing the fungal ribosomal gene sequences. Both groups find that the most highly evolved attine ants have a long history of coevolution with the fungi. Chapela *et al.* provide evidence that some of the more primitive ants may have repeatedly collected fungal symbionts.

A better mouse

Mice carrying inactivated alleles of the cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene have had limited utility as a model for CF because they die from intestinal obstructions shortly after birth. Zhou *et al.* (p. 1705) corrected

this lethal defect and prolonged survival of the mice by expressing a human CFTR transgene in the intestines of the mice. In



addition to providing a more viable animal model for CF, these results underscore the potential value of gene therapy for treating patients with CF.

Resetting the clock


Light resets the circadian clock, located in mammals in the suprachiasmatic nucleus (SCN), presumably by release of excitatory amino acids from neurons connected to the retina. Ding *et al.* (p. 1713) show that treatments of rat SCN with glutamate (Glu), N-methyl-D-aspartate (NMDA), or compounds that generate nitric oxide (NO) produced phase shifts in the circadian cycle similar to those induced by light. Antagonists of the NMDA and NO synthase pathways blocked the effects of Glu. Activation of NMDA receptors by Glu is the likely primary signaling event, followed by activation of NO biosynthesis.

Activation by reduction

One of the responses of plant and algal chloroplasts to illumination is increased synthesis of certain photosynthesis-related proteins. The increase is regulated at the level of translation of the mRNAs; the mRNAs available for translation are found complexed with RNA-binding proteins. Danon and Mayfield (p. 1717) found that formation of the complex in the alga *Chlamydomonas* is sensitive to redox potential. Reduction of a regulatory site on the RNA-binding protein activates its ability to bind *psbA* mRNA, while oxidation inhibits it. This type of interaction may provide a mechanism by which the reducing power generated by photosynthesis can regulate the amount of photosystem protein.

Parallel pathways

Binding of growth factors to their receptors initiates a complex series of biochemical reactions that leads to activation of transcription factors. Growth factor-dependent activation of the guanine nucleotide binding protein Ras leads to activation of cascades of protein kinases that sequentially activate one another. Minden *et al.* (p. 1719) show that activation of Ras turns on two such pathways. In one, the protein kinases Raf-1 and MEK and the mitogen-activated protein (MAP) kinases called ERKs are sequentially activated; in the other, a kinase called MEKK leads to activation of a different MAP kinase known as JNK. JNK and the ERKs participate in activation of different transcription factors. Thus, activation of these pathways may account for some of the complex transcriptional regulation that is caused by various growth factors.



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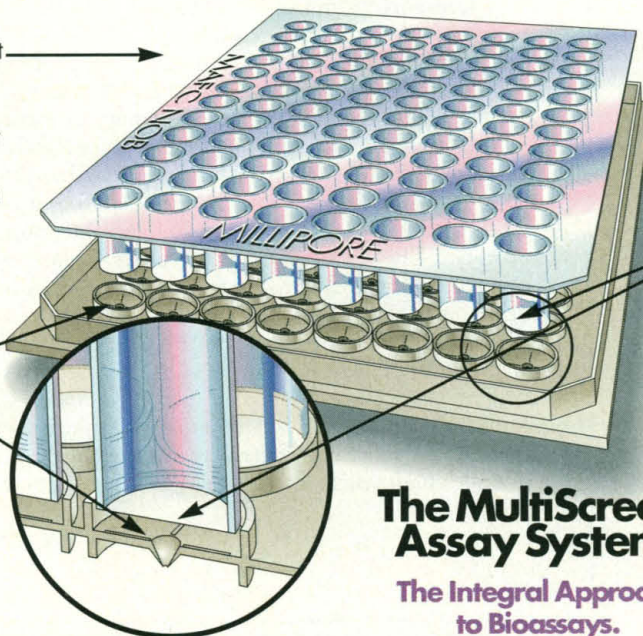


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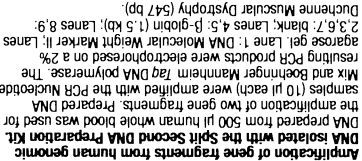
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Scientists have found that many of the optical microscopy techniques currently available are not well suited for the study of cellular dynamics inside living tissue.

Working with thinly cut sections of fixed tissue placed up against the cover glass, researchers are able to produce superb images using techniques such as confocal microscopy, DIC and epi-fluorescence. The problem arises when they try to study living cells *in vivo* or *in vitro* surrounded by physiological solution.

In the past, researchers have tried to achieve higher resolution by using plan apochromat or fluor high numerical aperture (NA) oil immersion objectives. This technique

works well when the details or events being studied are no more than 15 μ m below the cover glass, but cannot be used when the area of interest is 100 μ m to 200 μ m deep.

Spherical aberration is a problem

The problem is the different indexes of refraction of the oil and glass (1.515) and the aqueous physiological solution (1.33). The light rays are bent toward the higher refractive index at the glass interface, causing severe spherical aberration. This is seen as a loss of intensity and contrast, inability to collect and resolve small spatial frequencies and reduced accuracy of reproduction — all in direct proportion to how deep beneath the cover glass the area of interest lies.

Spherical aberration is especially troublesome in confocal imaging, a technique which is normally used to achieve increased resolution and narrow depth of field while eliminating out-of-focus light. In confocal systems, the illuminating pinhole is imaged on the specimen and a moving mirror mechanism scans the specimen in a raster pattern. The light emitted from the specimen is rescanned by the same mechanism and reimaged through the pinhole. Since only the light that passes back through the pinhole is imaged, all out-of-focus light is eliminated.

When scanning deep within a specimen using an oil immersion objective, spherical aberration can become so extreme that much of the

light coming back from the specimen is out of focus and unable to return through the pinhole.

Water immersion is the solution

This problem can be solved through the use of a water immersion objective. The refractive index of water closely matches that of both physiological solution and living cells, so that the effect of spherical aberration is dramatically reduced when looking deep within a specimen. Water also offers practical advantages because it will not fluoresce or contaminate physiological solution, and is easy to clean up.

Nikon has successfully produced a highly corrected water immersion 60x CFN plan apochromat objective with a 1.2 NA and a 220 μ m working distance. It has a correction collar that accommodates for cover glasses from 0.15mm to 0.18mm thick. This unique objective not only virtually eliminates spherical aberration, but is also chromatically corrected with high transmission in the near ultraviolet through the red spectrum, making it useful for confocal, fluorescence and DIC microscopy.

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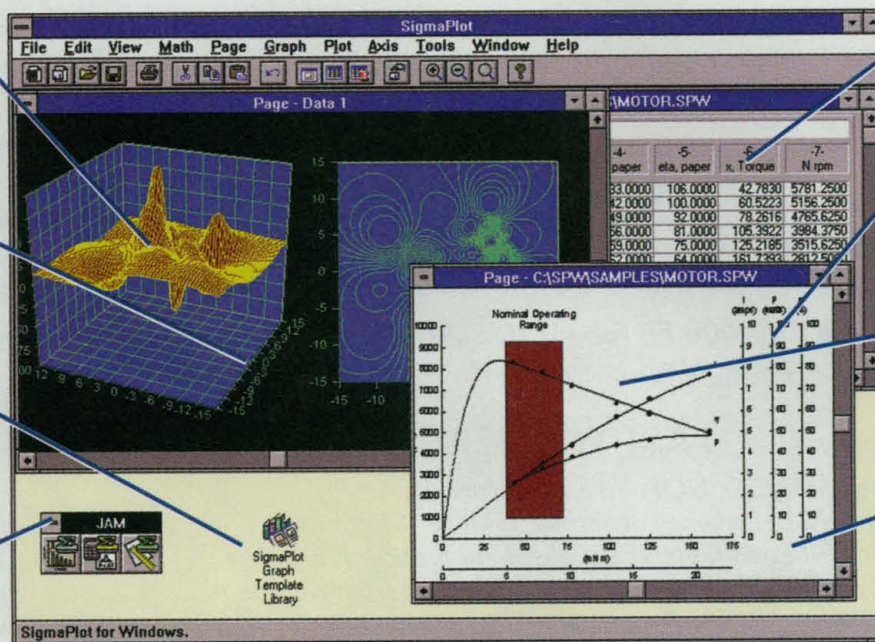
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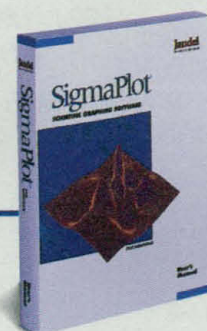
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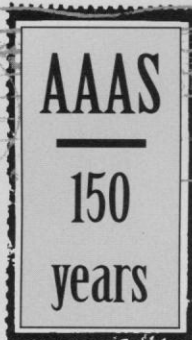


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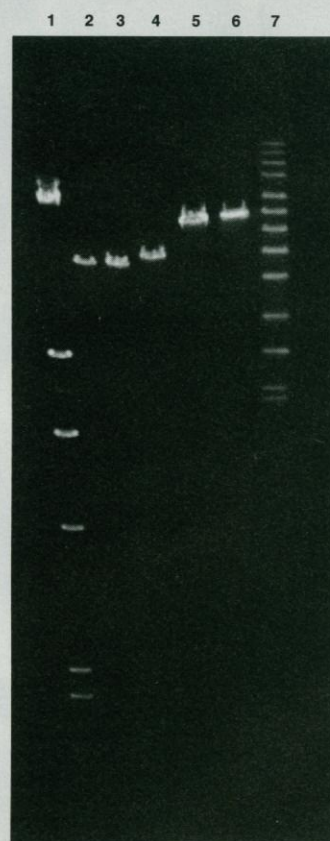
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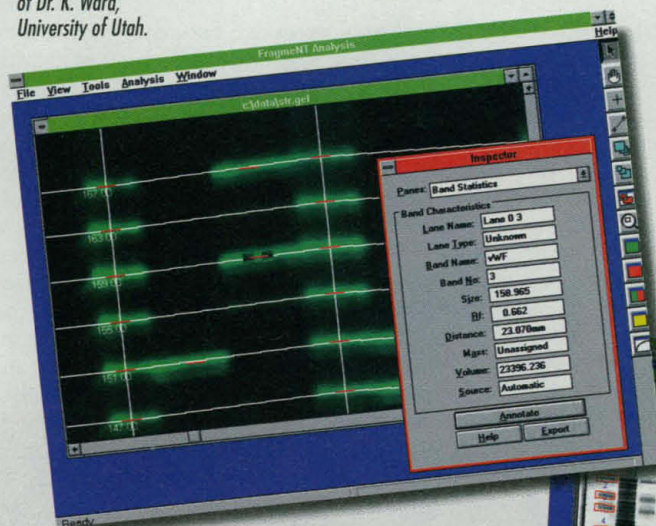
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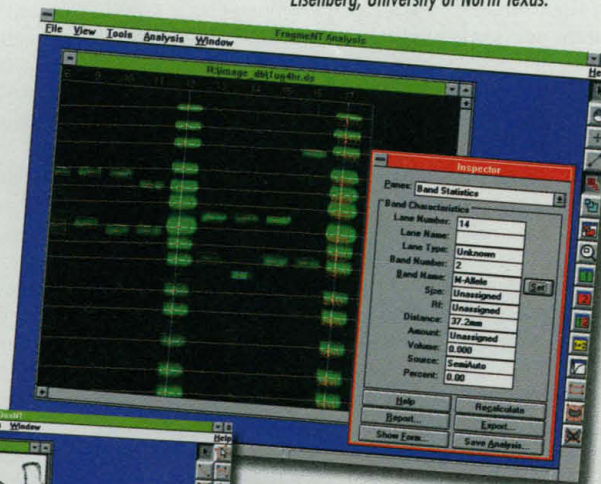


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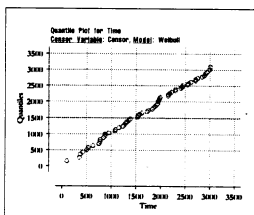
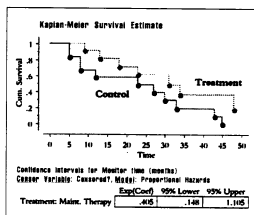
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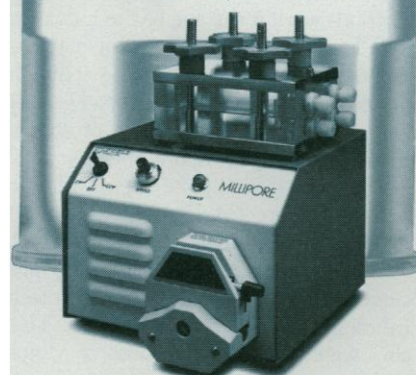
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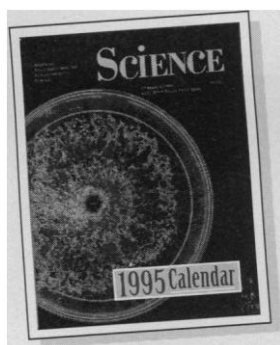
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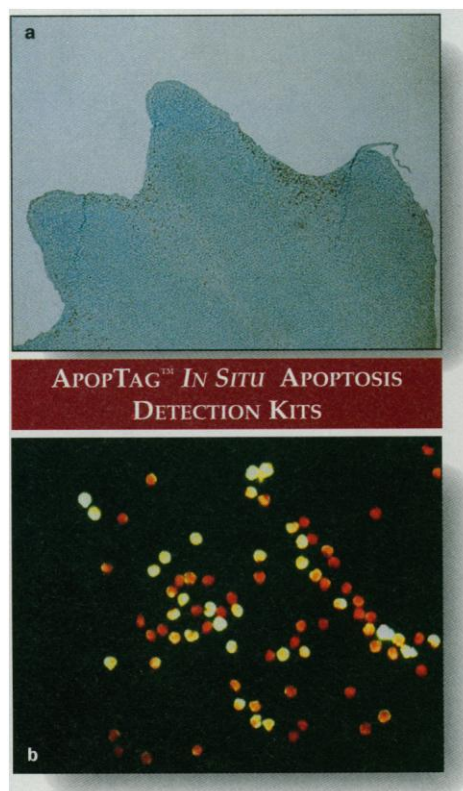
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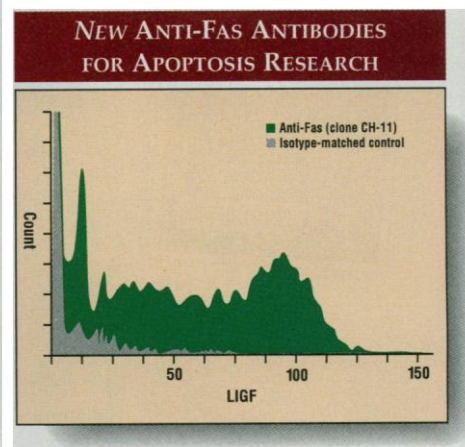


Apoptosis in 4-day post-weaning rat mammary gland (ApopTag™ Control Slide), Apoptag™ Peroxidase Kit and methyl green (X400)



a. Developmental cell deletion in remodeling of mouse forelimb bud (14-day embryo), Apoptag™ Peroxidase Kit and methyl green (X200)²

b. Apoptosis of human peripheral blood lymphocytes in vitro, Apoptag™ Fluorescein Kit (yellow) and propidium iodide (red) (X400)³



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¹ Yonehara, S., et al, (1989) *J. Exp. Med.* 169:1747-1756.

² JFR Kerr, J Searle, BV Harmon & CJ Bishop, in: Potten, CS (ed) (1987) *Perspectives in mammalian cell death.* Oxford U. Press, pp. 93-128. Z Zakeri, D Quaglino, T Latham & R Lockshin, (1993) *FASEB Journal*; 7:470-478; and manuscripts submitted.

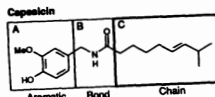
³ X Li, W James, F Traganos & Z Darzynkiewicz, (1993) manuscript submitted.

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Structure Activity Relationship Investigations with a Series of Capsaicin Analogues: The Hydrophobic Side-Chain "C-Region"

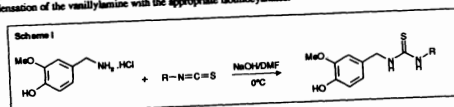
Introduction:

A series of analogues of capsaicin, the pungent principle of chilli peppers, was synthesized and tested for capsaicin-like agonism *in vitro*. A modular approach has been used to establish the structure-activity profile of specific capsaicin congeners and this report covers modifications made in the hydrophobic chain region ("C-region") as exemplified in the following diagram:

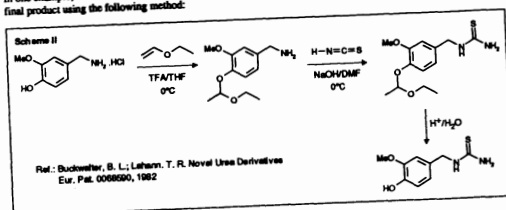


Synthesis:

The thioamides referenced in this report were all made by the following general route, which involves condensation of the vanillylamine with the appropriate isothiocyanate:



In one example, reference number 15f, it was necessary to protect the starting material and hence deprotect the final product using the following method:



Ref.: Buckwalter, B. L.; Latham, T. R. *Novel Urine Derivatives*
Eur. Pat. 0068590, 1982

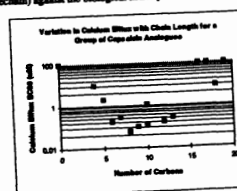
*Ref.: Analogues of Capsaicin with Agonist Activity as Novel Analgesic Agents; Structure-Activity Studies. 3. The Hydrophobic Side-Chain "C-Region". Christopher S.J. Walpole, Roger Wigglesworth, Stuart Swain, Elizabeth A. Campbell, Andy Day, Ian F. James, Ray J. Mason, Martin H. Perkins, and Janet Winter, J. Med. Chem., 1993, 36, 2381-2389

Analysis:

The following table illustrates the structures and activities of the most recent set of thioester capsaicin analogues with variation in the hydrophobic chain region ("C-region"):

Entry ID	R1	R2	R3	# of carbons	Ca ²⁺ (μM)
15f	-CH ₃	-CH ₃	-CH ₃	4	0.48
15g	-CH ₃	-CH ₃	-CH ₃	5	1.88
15h	-CH ₃	-CH ₃	-CH ₃	6	0.18
15i	-CH ₃	-CH ₃	-CH ₃	7	0.38
15j	-CH ₃	-CH ₃	-CH ₃	8	0.28
15k	-CH ₃	-CH ₃	-CH ₃	9	0.11
15l	-CH ₃	-CH ₃	-CH ₃	10	1.08
15m	-CH ₃	-CH ₃	-CH ₃	11	0.18
15n	-CH ₃	-CH ₃	-CH ₃	12	0.27
15o	-CH ₃	-CH ₃	-CH ₃	13	0.27
15p	-CH ₃	-CH ₃	-CH ₃	14	0.27
15q	-CH ₃	-CH ₃	-CH ₃	15	0.27
15r	-CH ₃	-CH ₃	-CH ₃	16	0.27
15s	-CH ₃	-CH ₃	-CH ₃	17	0.27
15t	-CH ₃	-CH ₃	-CH ₃	18	0.27
15u	-CH ₃	-CH ₃	-CH ₃	19	0.27
15v	-CH ₃	-CH ₃	-CH ₃	20	0.27

The data was used to produce the following graph which illustrates the relationship between the chain length (or number of carbons in the sidechain) against the biological activity in the calcium efflux assay:



Note the typical "bell-shaped" curve, with an optimum chain length of approximately 7-8 carbons. There is a notable outlying point at 10 carbons, which is less active than may be expected from the trend of the graph. This point represents the compound containing the adamantyl sidechain, which may be indicative of a bulk limitation in this region of the receptor binding pocket.

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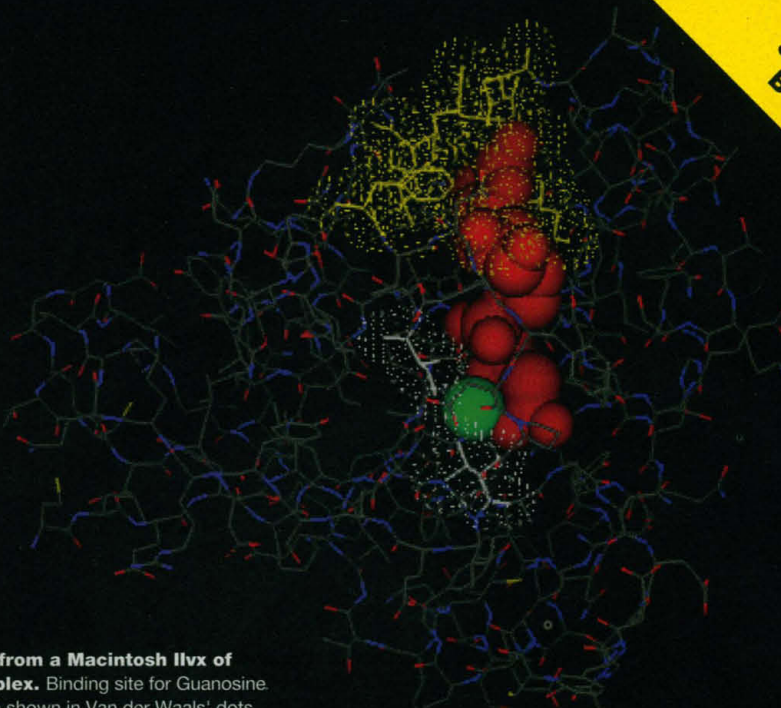
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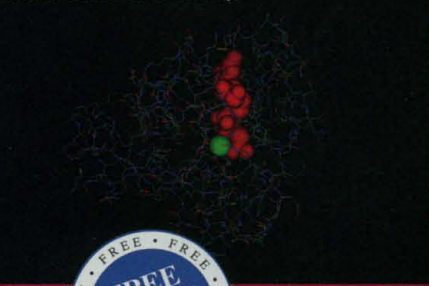
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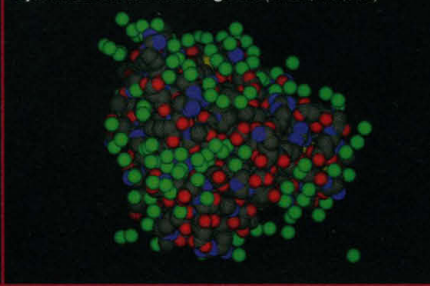


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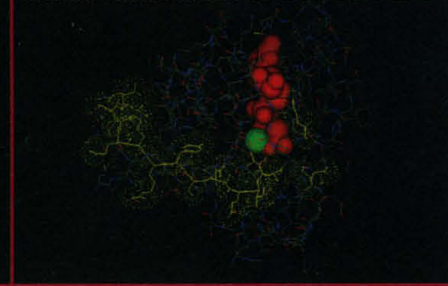
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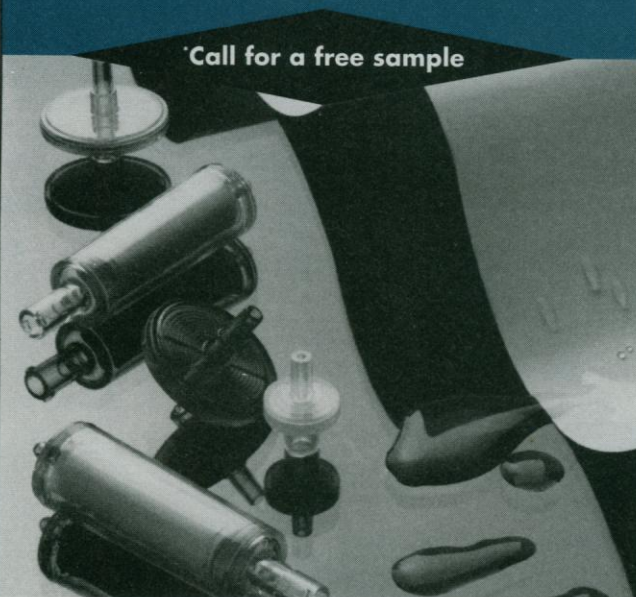
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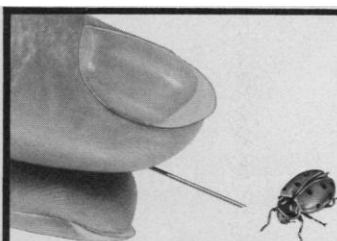
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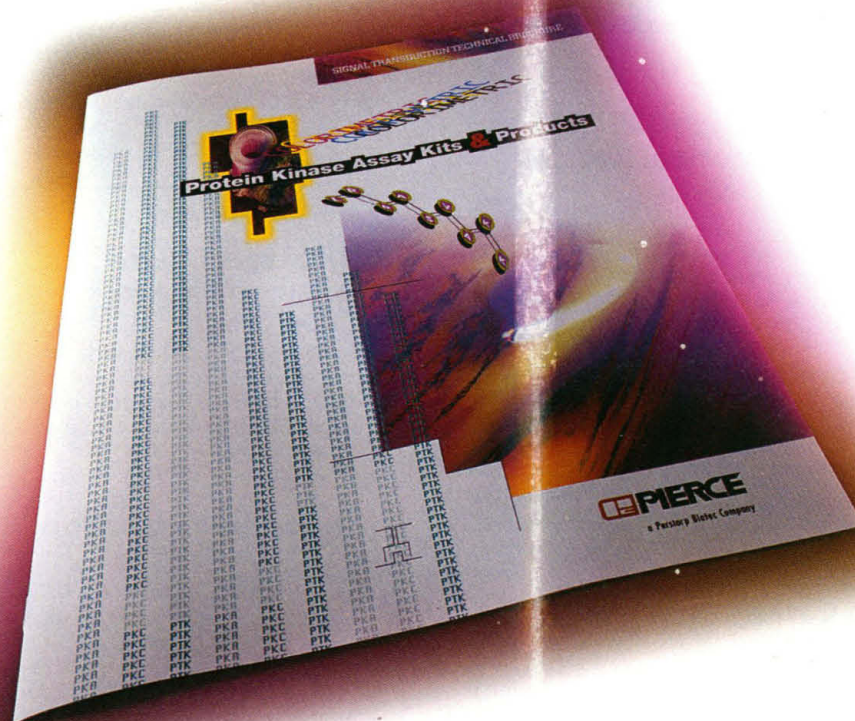
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